FULMINANT HEPATITIS: A CLINICAL REVIEW OF 11 YEARS

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SUMMARY

24 cases of fulminant hepatitis (FH) hospitalized in the Clínica de Doenças Infecciosas e Parasitárias do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo during the period from January 1976 to December 1986 were reviewed from their clinical, epidemiological and laboratorial aspects. 88% of the patients died; 20 patients (83%) presented hemorrhages and, of these, 19 died. Bacterial infections occurred in 14 patients (58%) all of whom died. Ascitis was noted in 3 cases; cerebral edema was present in 16 cases.

Maximal ALT levels for each patient during hospitalization ranged widely from 81 to 4,460 U/l/l. Thirteen patients presented high creatinine levels (54%). Prothrombin time activity ranged from 2.1% to 67%. Fever was present in 20 cases (83%). Encephalopathy occurred within the first 2 weeks of illness in 72% of the cases. In 7 cases other illnesses were present.

The etiology could not be determined in 13 cases. In 3 cases it was due to yellow fever and 6 cases were caused by viruses other than yellow fever. In one case the cause was drug usage and in another case, possibly alcohol.

The authors believe that the clinical definition of FH requires further discussion before it is established. In this study FH is a young person’s disease. The mortality found was similar to that by other authors. Factors that contributed to death were: hemorrhages and bacterial infection. Factors that worsened the prognosis of hepatitis were: associated illnesses and surgical procedure.

The levels of ALT during hospitalization did not correlate well with the severity of the hepatitis.

The authors believe that yellow fever should be considered a cause of FH where the clinical picture meets the criteria for such, although its mechanisms of encephalopathy remain obscure. The clinical details of the 3 cases of yellow fever are presented.

KEY WORDS: Fulminant hepatitis: Occurrence; Complications; Yellow fever.

INTRODUCTION

Fulminant hepatitis (FH) is a rare clinical syndrome which results from a massive destruction of hepatocytes and which can be considered a sudden severe liver malfunction without a previously known hepatopathy.17,18 It can be caused by various factors: virus, drugs (halothane, isoniazide, acetaminophen, alcohol), pregnancy, surgical shock, etc.18 The clinical definition of this syndrome is controversial; however the most accepted is
that of TREY — an acute severe hepatitis that leads to a severe hepatic encephalopathy within the first 8 weeks of illness.

Fulminant hepatitis is a highly lethal illness and its mortality varies according to different studies — 85.7%, 92.5%, 94%. Its prognosis is worsened by the following factors: pregnancy, undernourishment, previous surgery, old age.

The object of this study is to demonstrate different aspects of FH in Brazil — epidemiological, clinical and laboratorial. We believe this to be useful in view of the fact that few very studies have been made on this subject in our country.

**METHODS**

Through the hospital’s computerized registry system we made a survey of all the patients with diagnosis of hepatitis hospitalized in the Clínica de Doenças Infecciosas e Parasiárias do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, during the period from January 1976 to December 1986. Studying each of these cases 24 patients presented the clinical picture of FH based on TREY’s criteria. From these reports we collected all the information available on epidemiology (age, sex, use of blood or blood products, previous contact with hepatitis), clinical data (time of illness until the onset of encephalopathy, fever, duration of encephalopathy, complications, outcome), laboratorial data (aminotransferase levels, prothrombin time, kidney function, bilirubin levels, serology), and histological data (obtained through necropsy or biopsy).

The serologic tests for antibodies against hepatitis A virus (enzyme-linked immunosorbent assay) were incomplete as these tests were only initiated in 1985. A complete evaluation of hepatitis B virus infection (through the enzyme-linked immunosorbent assay and the radioimmunoassay) began in 1985 and previous to this date only HBsAg and anti-HBs were studied through radioimmunoassay. Before 1982 the only test used was complement fixation for the study of the Australia antigen.

Necropsies were performed in 20 cases and in 1 case a biopsy only was obtained. It was possible to review these results in only 5 cases.

The treatment given in all the cases of FH was supportive care as described by SHERLOCK.

**RESULTS**

Fourteen (58%) of the 24 patients with FH were male. Their distribution according to age can be seen in Figure 1 (mean age: 23 years). Twenty-one patients (88%) died. The 3 survivors refused liver biopsy during follow-up as outpatients and presented a complete clinical cure. Sixty-eight percent of the patients who died did so during the first month of illness (95 percent confidence interval: 48 to 88%).

The mean duration of the illness until the onset of encephalopathy was 16 days (range: 4 to 60 days) as can be seen in Figure 2. This information could be collected in 22 cases.

The lowest prothrombin time activity measured for each patient ranged from 2.1% to 67% of normal (mean: 17.38%). The highest creatinine level registered for each patient ranged from 0.5 to 14.7 mg/100 ml (mean: 4.3) and only 13 patients (54%) presented levels above 1.2 mg/100 ml. In these 13 cases the mean level was 6.42 mg/100 ml.

The highest aminotransferase levels registered for each patient ranged from 81 to 4,460 U/l (mean: 1,524) for alanine aminotransferase (ALT or SGTP) — Figure 3; and from 53 to 6,800 U/l (mean: 2,227) for aspartate aminotransferase (AST or SGOT). AST levels were retrieved in 22 cases. The upper ALT level was higher than the upper AST level in 10 cases and in 6 of these the ratio ALT/AST was above 1.5. The upper AST level was higher than the upper ALT level in 12 cases and the ratio AST/ALT was above 1.5 in 5 cases.

Fever was present in 20 cases (83%). Cerebral edema was present in 16 of the 21 patients who died (76%).

Hemorrhages occurred in 20 cases (83%) and of these the final outcome was fatal in 19 (95%). Secondary bacterial infections were encountered in 14 patients (58%) and in all of these cases the final outcome was death. The site of these infections can be seen in Figure 4.

Ascitis was noted in 3 of the 21 patients who died (14%).

In 7 fatal cases there were other illnesses concomitant with FH: neurocisticercosis,
carcinoma of the esophagus, chronic pancreatitis, hemophilia A, perforation of a duodenal ulcer on the day before death (this patient underwent surgery on this same day), pleural tuberculosis, and Hodgkin's lymphoma under chemotherapy.

The mean time of hospitalization among the patients who died was 11 days (range: 1 to 53); and the mean time among the 3 survivors was 22 days (11, 25 and 28 days respectively).

There is insufficient data to determine the etiology of all the cases. Three cases were caused by the yellow fever virus and 6 cases were attributed to other viruses (25%). Of these 6 cases one was caused by hepatitis A virus (this patient survived), 2 cases were caused by hepatitis B virus, and 3 cases were attributed to viruses (probably B virus) based on necropsy results and incomplete serologic data. The serology for antibodies against hepatitis A virus was performed in only 6 cases.

In one case, where FH was due to hepatitis B virus, the patient also had Hodgkin's lymphoma and had been receiving chemotherapy (vincristine, cyclophosphamide, prednisone and procarbazine) up to 20 days before the onset of the hepatitis. This patient died on the 8th day of the disease and on the 2nd day of encephalopathy. Another patient who had viral hepatitis took a hepatotoxic drug regularly (isoniazide).

In one case the cause was drug usage and this patient took carbamazepine, phenobarbital and diazepam regularly. In one case the possible cause of FH was alcohol abuse.

The data of the 3 cases caused by yellow fever can be seen on Table 1. All these patients had been on recent trips to areas of Brazil where this disease is endemic (Mato Grosso and Mato Grosso do Sul).

In 13 cases the cause of the hepatitis could not be clearly defined: one patient presented
Fig. 2 — Duration of illness until the onset of encephalopathy

Fig. 3 — Maximal ALT values registered
TABLE 1

Three yellow fever cases

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>24</th>
<th>27</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>male</td>
<td>male</td>
<td>male</td>
</tr>
<tr>
<td>Fever</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Time of illness until onset of encephalopathy</td>
<td>8 days</td>
<td>13 days</td>
<td>6 days</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>9 days</td>
<td>14 days</td>
<td>7 days</td>
</tr>
<tr>
<td>Drugs</td>
<td>alcohol</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Recent trips</td>
<td>M.T.</td>
<td>M.T.</td>
<td>M.S.</td>
</tr>
</tbody>
</table>

Laboratorial tests:
- Maximal AST: 2,400 > 3,000 1,900
- Maximal ALT: 520 > 4,000 1,600
- Maximal creatinine: 5.8 6.2 14.7
- Maximal total bilirubin: 14.8 9.4 11.8
- Minimal TP (%): 46 28 15

Complications:
- Cerebral edema: yes
- Hemorrhages:
  - digest.
  - lung
  - pancreas
  - kidney
  - biliary
  - muscle
- Secondary bacterial infections:
  - lung

M.T. = Mato Grosso
M.S. = Mato Grosso do Sul

Fig. 4 — Occurrence of secondary bacterial infection
TABLE 2

<table>
<thead>
<tr>
<th>Case</th>
<th>Etiology</th>
<th>Outcome</th>
<th>Other Conditions</th>
</tr>
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<tbody>
<tr>
<td>01</td>
<td>alcohol</td>
<td>death</td>
<td>chronic pancreatitis</td>
</tr>
<tr>
<td>02</td>
<td>unknown</td>
<td>death</td>
<td>carcinoma of the esophagus</td>
</tr>
<tr>
<td>03</td>
<td>viral*</td>
<td>death</td>
<td>Hodgkin's lymphoma, chemotherapy</td>
</tr>
<tr>
<td>04</td>
<td>unknown</td>
<td>death</td>
<td>hemophilia A, alcoholism</td>
</tr>
<tr>
<td>05</td>
<td>unknown</td>
<td>death</td>
<td>-</td>
</tr>
<tr>
<td>06</td>
<td>unknown</td>
<td>death</td>
<td>-</td>
</tr>
<tr>
<td>07</td>
<td>viral*</td>
<td>death</td>
<td>-</td>
</tr>
<tr>
<td>08</td>
<td>drug</td>
<td>death</td>
<td>-</td>
</tr>
<tr>
<td>09</td>
<td>unknown</td>
<td>death</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>yellow fever</td>
<td>death</td>
<td>alcoholism</td>
</tr>
<tr>
<td>11</td>
<td>yellow fever</td>
<td>death</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>unknown</td>
<td>survival</td>
<td>alcoholism</td>
</tr>
<tr>
<td>13</td>
<td>unknown</td>
<td>death</td>
<td>neurocisticercosis, dexamethasone</td>
</tr>
<tr>
<td>14</td>
<td>unknown</td>
<td>death</td>
<td>alcoholism</td>
</tr>
<tr>
<td>15</td>
<td>unknown</td>
<td>death</td>
<td>alcoholism</td>
</tr>
<tr>
<td>16</td>
<td>virus B</td>
<td>death</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>viral*</td>
<td>death</td>
<td>pleural tuberculosis, isoniazide</td>
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<td>18</td>
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<td>death</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>yellow fever</td>
<td>death</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>virus A</td>
<td>death</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>virus B</td>
<td>survival</td>
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</tr>
<tr>
<td>22</td>
<td>unknown</td>
<td>death</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>unknown</td>
<td>death</td>
<td>alcoholism</td>
</tr>
<tr>
<td>24</td>
<td>unknown</td>
<td>death</td>
<td>isoniazide, surgery for a perforated ulcer</td>
</tr>
</tbody>
</table>

( * ) Cases attributed to viruses based on necropsy results and incomplete serologic data.

HBsAg in the serum and 2 were positive for anti-HBs; 5 drank alcohol regularly; one took isoniazide regularly; and one patient had undergone treatment for neurocisticercosis with dexamethasone and praziquantel.

The results of the necropsy and biopsy studies were: acute alcoholic hepatitis in one case; massive liver necrosis in 9 cases; submassive liver necrosis in 5 cases; acute hepatitis in 3 cases; yellow fever in 3 cases.

**DISCUSSION**

There are different accepted definitions of FH although the most used is that of TREY21 which includes all acute cases of hepatitis that lead to severe hepatic encephalopathy within the first 8 weeks of illness (with a presumed normal liver function prior to the disease). Other authors believe that the period concerned should be shorter: 4 weeks10,11. In our study 72% of the patients presented encephalopathy during the first 2 weeks of illness (95 percent confidence interval: 54 to 90%). We believe this matter deserves a great deal more discussion before it is established.

In our study 75% of the patients were under 30 years of age (95 confidence interval: 59 to 91%). This would indicate that in our environment FH is a young person's disease, contrary to what has been reported in some other studies9,11,16.

Mortality in our study was 88% similar to results obtained in other studies3,16,23. Our findings are also similar to those of other reports where illnesses concomitant with FH worsened the outcome. Factors that could contribute to death are: hemorrhages, cerebral edema, secondary bacterial infections, renal failure, pancreatitis, pulmonary and circulatory failure18. All our patients who presented
secondary bacterial infections died (14 cases) and only one of the 20 patients who presented hemorrhages survived. In 7 patients there were other illnesses associated with FH, and in all these cases the final outcome was fatal.

There have been reports of cancer patients treated with chemotherapy who presented FH caused by the hepatitis B virus (HBV) after withdrawal of immunossupression. One of our patients had Hodgkin's lymphoma which was treated with chemotherapy until 20 days before the onset of FH (positive for Australia antigen). Another patient had received dexamethasone over a long period (1.5 months) during treatment for neurocisticercosis and received also praziquantel before presenting FH. It was not possible to determine the etiology of this hepatitis.

Another factor which could negatively affect the prognosis of hepatitis is surgical procedure. This event occurred in one of our cases where a patient with hepatitis was submitted to emergency surgery for a perforated gastric ulcer. The following day the patient presented hepatic encephalopathy and died.

It is difficult to establish the influence of hepatotoxic drugs in worsening the outcome of the disease when these are associated with viral hepatitis. In one of our cases of FH this association was present (the patient took isoniazide regularly).

Although a complete follow-up of the survivors was not possible, they presented a clinical cure. We believe that the majority of the survivors of FH will have a complete cure and only rarely will chronic hepatitis develop.

In our study ascitis was present in 3 of the 21 patients who died. LEBREC et al. described a high occurrence of ascitis in FH, as opposed to what occurs in other forms of acute viral hepatitis. This could be explained by the presence of portal hypertension and by the sodium retention that occurs in FH. Our findings are similar to those of other authors.

Fifty percent of our patients presented very high alanine aminotransferase (ALT) levels (above 1,500 UI/l) during hospitalization (95 percent confidence interval: 30 to 70%). Thus it is not possible to assert that the ALT values obtained during hospitalization correlate to the severity of the hepatitis. The upper AST level for each patient varied widely in relation to the upper ALT level and no trend could be determined.

The etiology of FH in our cases was made difficult to determine by the absence of serologic data. It is important however to remember the possibility of an increase in the severity of hepatitis when more than one virus is involved. In our cases nothing could be substantiated in this respect.

Our three yellow fever cases were considered FH because they met the clinical criteria for such. In yellow fever the physiopathological mechanisms of encephalopathy are unknown. Many factors may play a role: hipotension, acidosis, hypoglicemia, altered concentrations of aminoacids and neurotransmitters. In experimental studies the virus was not found to invade the brain. These three patients had visited areas of Brazil where yellow fever is endemic (Mato Grosso and Mato Grosso do Sul) and had contact with the forest. This transmission of yellow fever should be considered 'sylvatic' (monkey-mosquito-human) and not 'urban' (interhuman).

In all three cases complications developed that probably worsened the prognosis and could be related to their fatal outcome: severe hemorrhages, renal failure, coma, very high levels of serum aminotransferase. The definite diagnosis was made through necropsy and histopathologic examination of the liver.

**RESUMO**

**Hepatite fulminante: uma retrospectiva clínica de 11 anos**

Vinte e quatro casos de hepatite fulminante (HF), internados na Clínica de Doenças Infecciosas e Parasitárias do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo durante o período de janeiro de 1976 a dezembro de 1986, foram revistos para a obtenção de dados clínicos, epidemiológicos e laboratoriais.

88% dos pacientes morreram. Vinte (83%) dos pacientes apresentaram hemorragias, dentre os quais 19 morreram (95%). Infeções bacterianas secundárias ocorreram em 14 pacientes (58%) todos os quais faleceram. Ascite foi notada em 3 casos e edema cerebral em 16 casos. Os valores máximos de ALT obtidos para cada
paciente durante a internação variaram de 81 a 4.460 UI/l. Treze pacientes tiveram elevação de creatinina (54%). A atividade do tempo de protrombina variou de 2,1% a 67%. A febre esteve presente em 20 casos (83%). A encefalopatia surgiu durante as 2 primeiras semanas de doenças em 72% dos casos. Em 7 casos havia doenças associadas à hepatite.

A etiologia não pode ser determinada em 13 casos; 3 casos foram por febre amarela; e 6 casos por outros vírus. Em 1 caso a causa foi drogas e em um caso, possivelmente, foi álcool.

Os autores acreditam que a definição de HF merece discussão antes de ser totalmente aceita. Neste estudo, a HF foi uma doença que acometeu principalmente jovens. A letalidade encontrada foi semelhante a de outros estudos. Fatores que contribuíram para o óbito foram hemorragias e infecções bacterianas secundárias. Fatores de piora do prognóstico da hepatite foram a presença de outras doenças associadas e de procedimento cirúrgico.

Os níveis de ALT durante a internação não refletiram a gravidade da hepatite.

Os autores acreditam que a febre amarela deve ser considerada um agente etiológico de HF.

Os dados clínicos dos 3 casos de febre amarela encontrada foi semelhante a de outros estudos.

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